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10/560,482	12/12/2005	Frans Eduard Janssens	PRD2077f-PCT-USA	3160

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EXAMINER	
BAEK, BONG-SOOK	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,482	JANSSENS ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9-14 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *9 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

The amendment filed on November 13, 2008 is acknowledged. Claims 2-8 and 15-20 have been canceled and claims 9 and 21-26 have been withdrawn. Claims 1 and 10-14 are under examination in the instant office action.

Applicants' arguments, filed on November 13, 2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Responses are limited to Applicants' arguments relevant to either reiterated or newly applied rejections.

Rejections maintained

The following rejections of the claims are maintained for reasons of record and the following.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

1) Claims 1 and 10-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/25988 (publication date: 7/24/1997) in view of US patent 6,197,772 B1 (issue date: 3/6/2001).

The instant invention is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier, an opioid analgesic (elected species: fentanyl), and 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives represented by formula (I) (elected species: (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid). In other embodiments, the composition is formulated for simultaneous, separate or sequential use (claim 11) and is orally administered (claim 14).

WO 97/25988 teaches a pharmaceutical composition comprising a compound with tachykinin antagonist activity including NK_1 receptor antagonist activity and non-tachykinin receptor antagonist analgesic including fentanyl, together with at least one pharmaceutically acceptable carrier, diluents or excipient for the treatment or prevention of pain or nociception (abstract; p7, 1st paragrph; p31, last paragraph; p32; and p44, 1st compound). WO 97/25988

further teaches that the composition can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal (p48, 1st paragraph) and the administration of the non-tachykinin receptor antagonist analgesic may be simultaneous with, before, or after the administration of the tachykinin receptor antagonist (p58, 5th paragraph). These teachings read on limitations recited in the instant claims 11 and 14. In addition, WO 97/25988 discloses that the combination therapy is advantageous because a marked decreased amount of a traditional analgesic can be administered, which would lessen the likelihood and severity of any adverse effects (p47, 2nd paragraph). The reference differs from the instant claims insofar as it does not teach 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives recited in claim 1 including the elected species, (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid.

US patent 6,197,772 B1 teaches the same generic chemical structure of 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives represented by formula (I) and (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as a preferable embodiment as recited in the instant claims 1 and 10 (column 1, line 44-column 4, line 23; column 7, line 39-column 8, line 5; claims 1-3). In addition, US patent 6,197,772 B1 teaches that 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives have tachykinin antagonistic activity, in particular substance P (NK_1 receptor agonist) antagonistic activity (column 1, lines 9-14) and can be used for the treatment of pain, emesis, or asthma (column 18, lines 33-44).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of WO 97/25988 with the teachings of US patent 6,197,772 B1 for the treatment of pain and/or nociception because of the following reasons: according to WO 97/25988, the pharmaceutical composition comprising a NK_1 receptor antagonist and a non-tachykinin receptor antagonist analgesic such as fentanly is effective on the treatment or prevention of pain or nociception and possible side effects of other analgesics. US patent 6,197,772 B1 teaches (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as NK_1 receptor antagonist. Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to be motivated to substitute one NK_1 receptor antagonist in the prior art with another NK_1 receptor antagonist such as (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid for the combination with a opioid analgesic in order to provide the same effect.

Response to Applicants' arguments:

Applicants argued that neither Iyengar *et al.* or Janssens *et al.* suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids and the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record.

However, they are not deemed to be persuasive. The alleged unexpected effect of "reduced respiratory depression" is not claimed as a range or by functional language, so Applicant's possible unexpected result is not commensurate with the scope of the claimed

invention. In addition, a mere statement of unexpected result without showing any comparative study or evidence is not considered to be persuasive.

2) Claims 1 and 10-13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent 5,880,132 (issue date: 3/9/1999) in view of US patent 6,197,772 B1.

US patent 5,880,132 teaches a pharmaceutical composition comprising a tachykinin antagonist in paricular an NK_1 receptor antagonist and an opoid analgesic, together with at least one pharmaceutically acceptable carrier or excipient for the treatment or prevention of pain or nociception (abstract; column 1, lines 7-10; and column 2, lines 33-36). US patent 5,880,132 defines that the term opioid is generally accepted to refer in a generic sense to all drugs, natural or systhetic with morphone-like action (column 1, line 52-56), which encompasses fentanyl. US patent 5,880,132 further teaches that the composition may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of pain (column 2, lines 42-46 and claim 4). This teaching reads on the limitations recited in instant claim 11. In addition, US patent 5,880,132 discloses that the composition is possible to treat pain with a sub-maximal dose of an opioid analgesic thereby reducing the likelihood of side-effects associated with opioid analgesic usage such as nausea, vomiting, and tolerance. The reference differs from the instant claims insofar as it does not teach 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives recited in claim 1 including the elected species, (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid.

US patent 6,197,772 B1 teaches the same generic chemical structure of 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives represented by formula (I) and (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as a preferable embodiment as recited in the instant claims 1 and 10 (column 1, line 44-column 4, line 23; column 7, line 39-column 8, line 5; claims 1-3). In addition, US patent 6,197,772 B1 teaches that 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives have tachykinin antagonistic activity, in particular substance P (NK_1 receptor agonist) antagonistic activity (column 1, lines 9-14) and can be used for the treatment of pain, emesis, or asthma (column 18, lines 33-44).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of US patent 5,880,132 with the teachings of US patent 6,197,772 B1 for the treatment of pain and/or nociception because of the following reasons: according to US patent 5,880,132, the pharmaceutical composition comprising NK_1 receptor antagonist and an opoid analgesic is effective on the treatment or prevention of pain or nociception and possible side effects of opoid analgesics. US patent 6,197,772 B1 teaches a (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as NK_1 receptor antagonist. Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to be motivated to substitute one NK_1 receptor antagonist in the prior art with another NK_1 receptor antagonist in the instant invention for the combination with a opioid analgesic in order to provide the same effect.

Response to Applicants' arguments:

Applicants argued that neither Hill or Janssens *et al.* suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids and the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record.

However, they are not deemed to be persuasive. The alleged unexpected effect of "reduced respiratory depression" is not claimed as a range or by functional language, so Applicant's possible unexpected result is not commensurate with the scope of the claimed invention. In addition, a mere statement of unexpected result without showing any comparative study or evidence is not considered to be persuasive.

3) Claims 1 and 10-13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent application publication 2002/0052504 (publication date: 5/2/2002) in view of US patent 6,197,772 B1.

US patent application publication 2002/0052504 teaches a pharmaceutical composition comprising a piperidine derivative having a potent NK_1 receptor antagonist activity in combination with other analgesics such as opioid anangegics inlcuding fentanyl, together with at least one pharmaceutically acceptable carrier or excipient for the treatment or prevention of pain or nociception ([0002], [0076] and [0077]). US patent application publication 2002/0052504 further teaches the composition as a combined preparation for simultaneous or separate, or sequential use in the treatment or prevention of pain or nociception ([0078]). This teaching read on the instant claim 11. The reference differs from the instant claims insofar as it does not teach 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives recited in claim 1 including

the elected species, (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid).

US patent 6,197,772 B1 teaches the same generic chemical structure of 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives represented by formula (I) and (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as a preferable embodiment as recited in the instant claims 1 and 10 (column 1, line 44-column 4, line 23; column 7, line 39-column 8, line 5; claims 1-3). In addition, US patent 6,197,772 B1 teaches that 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives have tachykinin antagonistic activity, in particular substance P (NK_1 receptor agonist) antagonistic activity (column 1, lines 9-14) and can be used for the treatment of pain, emesis, or asthma (column 18, lines 33-44).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of US patent application publication 2002/0052504 with the teachings of US patent 6,197,772 B1 for the treatment of pain and/or nociception because of the following reasons: US patent application publication 2002/0052504 teaches the pharmaceutical composition comprising a NK_1 receptor antagonist and an analgesic such as fentanyl is effective on the treatment or prevention of pain or nociception. US patent 6,197,772 B1 teaches (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N-(2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as NK_1 receptor antagonist. Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to be motivated to substitute one NK_1 receptor antagonist in the prior art with another NK_1 receptor antagonist such as (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-

piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid for the combination with a opioid analgesic in order to get the same effect.

Response to Applicants' arguments:

Applicants argued that neither Elliott or Janssens *et al.* suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids and the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record.

However, they are not deemed to be persuasive. The alleged unexpected effect of "reduced respiratory depression" is not claimed as a range or by functional language, so Applicant's possible unexpected result is not commensurate with the scope of the claimed invention. In addition, a mere statement of unexpected result without showing any comparative study or evidence is not considered to be persuasive.

4) Claims 1 and 10-13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US patent 6,136,824 (issue date: 10/24/2000) in view of US patent 6,197,772 B1.

US patent 6,136,824 teaches a pharmaceutical composition comprising a piperidine-propan-2-derivative having a potent NK_1 receptor antagonist activity in combination with other analgesics such as opioid analgesics inlcuding fentanyl, together with at least one pharmaceutically acceptable carrier or excipient for the treatment or prevention of pain or nociception (column 1, line 63-column 2, line 2 and column 11, line 4-34). US patent 6,136,824 further teaches the composition as a combined preparation for simultaneous or separate, or sequential use in the treatment or prevention of pain or nociception (column 11, line 35-39). This

teaching read on the instant claim 11. The reference differs from the instant claims insofar as it does not teach 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives recited in claim 1 including the elected species, (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid).

US patent 6,197,772 B1 teaches the same generic chemical structure of 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives represented by formula (I) and (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as a preferable embodiment as recited in the instant claims 1 and 10 (column 1, line 44-column 4, line 23; column 7, line 39-column 8, line 5; claims 1-3). In addition, US patent 6,197,772 B1 teaches that 1-(1, 2-disubstituted piperidinyl)-4-substituted piperazine derivatives have tachykinin antagonistic activity, in particular substance P (NK_1 receptor agonist) antagonistic activity (column 1, lines 9-14) and can be used for the treatment of pain, emesis, or asthma (column 18, lines 33-44).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of US patent 6,136,824 with the teachings of US patent 6,197,772 B1 for the treatment of pain and/or nociception because of the following reasons: US patent 6,136,824 teaches the pharmaceutical composition comprising a NK_1 receptor antagonist and an analgesic such as fentanly is effective on the treatment or prevention of pain or nociception. US patent 6,197,772 B1 teaches (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid as NK_1 receptor antagonist. Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to be motivated to substitute one NK_1 receptor

antagonist in the prior art with another NK_1 receptor antagonist such as (B)-trans-4-[1-[3,5-bis (trifluoromethy) benzoyl]-2-(phenymethy)-4-piperidiny]-N- (2,6-dimethylphenyl)-l-piperazine acetamide, (L)-malic acid for the combination with a opioid analgesic in order to provide the same effect.

Response to Applicants' arguments:

Applicants argued that neither MacLeod *et al.* or Janssens *et al.* suggest or disclose that NK1 antagonists can reduce the level of respiratory depression caused by opioids and the presently claimed composition unexpectedly provides reduced respiratory depression, which was not previously recognized by the prior art of record.

However, they are not deemed to be persuasive. The alleged unexpected effect of "reduced respiratory depression" is not claimed as a range or by functional language, so Applicant's possible unexpected result is not commensurate with the scope of the claimed invention. In addition, a mere statement of unexpected result without showing any comparative study or evidence is not considered to be persuasive.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00-6:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614
Bbs

BONG-SOOK BAEK
Examiner, Art Unit 1614